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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/630,846	08/02/2000	James D. Thompson	030206.0179.CON1	8327

20306 7590 05/21/2002

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EXAMINER

LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 05/21/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/630,846

Applicant(s)

THOMPSON, JAMES D.

Examiner

Karen A. Lacourciere

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Application/Control Number: 09/630,846
Art Unit: 1635

Page 2

DETAILED ACTION

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(1). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text. It is noted that Applicant states that a copy of the abstract on a separate sheet was submitted with the response filed 02-22-02, however, that abstract does not appear to have been received in the Office.

Terminal Disclaimer

The terminal disclaimer filed on 02-22-02 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 5,902,880 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on 02-22-02 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,146,886 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

The rejections of record under 35 U.S.C. 112, second paragraph, have been withdrawn in response to Applicant's amendments filed 02-22-02.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1635

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are maintained as rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of introducing an RNA molecule into a cell in vitro (cell culture), does not reasonably provide enablement for a method of introducing an RNA molecule into a cell in vivo (whole organism) nor does the specification reasonably provide enablement for a transcribed RNA molecule which comprises a therapeutic portion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the prior Office action, mailed 11-05-01. This rejection is as follows.

Claims 1-17 and 20-25 are drawn to a transcribed RNA molecule wherein the RNA comprises a therapeutic portion. Claims 18 and 19 are drawn to a method of providing a desired RNA molecule to a cell, wherein the RNA molecule is transcribed, including from a vector. These claims encompass methods of introducing an RNA molecule into a cell in vitro (cell culture) or in vivo (whole organism).

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification has provided examples wherein Applicant has demonstrated transfer of an RNA molecule to a cell in vitro (cell culture), however, the specification clearly indicates that the claimed methods would encompass the transfer of an RNA molecule to a cell in vivo (whole organism) for therapeutic purposes (ie. gene therapy). The specification does not provide any examples wherein an RNA molecule is provided to a cell in vivo (whole organism). Further, these claims are drawn to transcribed RNA molecules wherein the RNA molecule comprises a therapeutic portion, however, the specification has not provided any examples of RNA molecules which have therapeutic properties.

At the time the instant invention was made, and even to date, gene therapy methods are highly unpredictable, particularly with regard to the delivery of an RNA molecule or vector to a cell and expression from said vector (see for example Orkin et al., Anderson, Verma et al.) and in vitro methods typically do not translate into success in vivo. Further, even if a molecule can be successfully delivered into a cell, to result in a therapeutic effect the expression of the oligonucleotide must be sufficient to provide the therapeutic effect or block the expression of a gene. The level of expression required varies dependent upon the disease state which is treated.

Expression of vectors *in vivo* (whole organism) is unpredictable, often too low for therapeutic effects or unexpectedly turned off (see Verma et al., for example). Effective expression requires an appropriate promoter-enhancer combination, "the search for such combinations is a case of trial and error for a given type of cell" (see Verma, for example, p 240). Applicant has not provided any guidance as to how to deliver their oligonucleotide to a specific target cell in vivo or whether their promoter would result in sufficient expression in any target cell to provide a therapeutic effect. The amount of experimentation to make an use the claimed

Art Unit: 1635

method to provide an RNA to a cell in vivo (whole organism), or provide a therapeutically effective RNA is very high. Due to the lack of specific guidance, one skilled in the art would need to practice undue trial and error experimentation to practice the methods of delivery, as claimed, over the full scope claimed. This experimentation would require the determination of how to specifically deliver the claimed RNA molecule, or a vector expressing such, to a target cell in vivo (whole organism), or provide said RNA as a therapeutic molecule.

Therefore, due to the broad breadth of the claims, the nature of the invention, the high unpredictability of the art, the lack of sufficient guidance provided by the inventor, the lack of working examples, and the quantity of experimentation required, it would have required undue trial and error experimentation for one skilled in the art to practice the invention as claimed, over the full scope claimed.

Response to Arguments

Applicant's arguments filed 02-22-02 have been fully considered but they are not persuasive. Applicant argues that the instant specification provides examples wherein one ribozyme of the invention is transformed into one human cell line in vitro and that methods of transforming cells in culture were well known at the time of the invention and that this is sufficient to enable the claimed invention. Applicant further argues that enablement does not require disclosure of an example if the disclosure is sufficient such that one skilled in the art will be able to practice it without undue experimentation. Applicant further argues, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate*" and

Art Unit: 1635

that exact correlation is not required. Applicant points to pages 15-22 of the specification to support the assertion that the claims are enabled for in vivo applications. Applicant states that cell in culture expressed one ribozyme even after 3 months. Applicant points to several post-filing references to support that certain embodiments of the claimed invention were successfully delivered to cells in vivo. Applicant argues that the experimentation required would be routine to make the instantly claimed invention over the full scope claimed.

These arguments have not been found to be persuasive because the specification as filed has not provided any guidance to overcome the art recognized hurdles to the application of ribozyme therapy in vivo (whole organism). The methods of transforming cells *in vitro* disclosed in the specification and the prior art, which Applicant relies upon to support the enablement of their claimed methods, would not provide guidance for delivery of an RNA molecule in vivo. For example, Applicant points to pages 21-22 of their specification. This provides an example wherein the ribozyme of the example has been transduced into cells in vitro, however, there is no information on how that was actually done, nor any information on how to adapt that transduction to apply to cells in vivo. Applicant further points to refers to Sambrook et al. and Uhlmann et al., which are concerned only with in vitro transformation methods and does not provide guidance on in vivo delivery. Applicant mentions cationic lipids for exogenous delivery (Malone et al.), however, these methods are also not applicable to in vivo delivery. In vitro methods for delivery of nucleic acids were not recognized in the art as correlating to in vivo delivery for nucleic acids. Further, the Examiner has provided references which point out the limitations which prevent one skilled in the art from practicing the claimed methods through routine experimentation. The standard for enablement is not whether one

Art Unit: 1635

skilled in the art *will* be able to practice the claimed invention, but whether one skilled in the art would have been able to practice the claimed methods *at the time of filing*. The post-filing references provided by Applicant do not demonstrate that the claimed invention was enabled at the time of filing. Further, the post-filing references provided by Applicant do not utilize methods or guidance provided by the specification and, further, would not support the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 9-12, 15-19, 24 and 25 are maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Inouye (US Patent No. 5,208,149).

Inouye discloses a non-naturally occurring RNA molecule which comprises an intermolecular stem structure of more than 8 bases and wherein the RNA comprises an antisense molecule, wherein the RNA is encoded by a vector and in a cell and wherein the RNA is separated from the intramolecular stem by a spacer region. Inouye disclose their RNA as comprising a therapeutic portion (e.g. to block the expression of harmful genes, such as oncogenes and viral genes). Therefore, Inouye anticipates claims 1, 9-12, 15-19, 24 and 25.

Claims 1, 2, 9-19, 21, 24 and 25 are maintained as rejected under 35 U.S.C. 102(e) as being anticipated by Noonberg et al. (US Patent No. 5,624,803).

Noonberg et al. disclose RNA polymerase based constructs for generating oligonucleotides wherein the construct comprises a U6 RNA polymerase III promoter, and a region comprising a desired RNA, including a therapeutic RNA (for example, antiviral or anticancer) and wherein the RNA comprises a region of complementarity between a 5' region and a 3' region (intramolecular stem region) which is generally between about 8 and about 30 nucleotides in length (see for example col 15, lines 45-50). The RNA disclosed by Noonberg et al. includes an RNA which comprises an antisense oligonucleotide, a ribozyme, a triplex-forming molecule or combination (see for example col 14, lines 60-64). The RNA disclosed by Noonberg et al. is transfected into cells (see for example col 23, lines 35-67). Therefore, Noonberg et al. anticipates claims 1, 2, 9-19, 21, 24 and 25.

Response to Arguments

Applicant's arguments filed 02-22-02 have been fully considered but they are not persuasive. Applicant argues that Inouye does not anticipate the claimed invention because Inouye discloses RNA molecules with terminal stem loop structures.

Applicant's arguments are not persuasive because the RNA molecules disclosed by Inouye would be encompassed by the instantly claimed invention and Applicant has not pointed out any limitations in the claim which are not met by the RNA molecule disclosed by Inouye. The RNA molecule disclosed by Inouye comprises the intramolecular stem of the claimed invention and the therapeutic portion of the RNA disclosed by Inouye is between the 3' region of the molecule and 5' complementary nucleotides in the 5' terminal stem loop.

Applicant argues that Noonberg et al. is a continuation-in-part and that the priority document for Noonberg et al. does not disclose the claimed invention, therefore, Noonberg et al. is not prior art to the claims. Applicant states that the priority document for Noonberg et al. discloses "small double-stranded hairpin loops" and does not disclose a lariat structure. These arguments have not been found to be persuasive because the claims do not recite a lariat structure, nor is a lariat structure required to meet the limitations of the claimed invention. The double strand hairpins disclosed in the priority document for Noonberg et al. meet the limitations of the claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after

Art Unit: 1635

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
May 19, 2002



ANDREW WANG
PRIMARY EXAMINER